| ORM.PTO-1 | 449 . | | | | ATTY. DOCK 030727.0027 | IO. | | IAL NO. -978,45 | |
|---------------------------------------|------------|-------------------------------------|-----------|------------|---------------------------|------|-----|--------------------|----------------|
| | FORMA | S AND OTHER ITEM TION DISCLOSURE | STATEMENT | | APPLICANT: ERION | CONT | | -970,43 | 4 |
| , O 1 A | (Use | several sheets if ne | ecessary) | | FILING DATE: 10/15/01 | | GRO | UP: | 016 |
| B B B B B B B B B B B B B B B B B B B | 8 | | | | | | | COPY OF F | |
| POEMARK OFFI | 7 . | | U.S. P | ATENT DO | CUMENTS | | | | |
| EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | | NAME | CLAS | s | SUB CLASS | FILING DATE |
| 10 | AA | 3,018,302 A | 01.23.62 | Bielefeld, | et al. | | | _ | |
| Pa | AB | 5,658,889 | 08/19/97 | GRUBER, | et al. | 514 | } | 43 | 12/14/94 |

| | | | FOREIGN | PATENT DOCUMENTS | | | |
|---------------------|------|--------------------|----------|------------------|--------|--------------|-------------------|
| EXAMINER INITIAL | | DOCUMENT NUMBER | DATE | COUNTRY | CLASS. | SUB CLASS | TRANSLAT YES N |
| to) | AC | 91 19721 A1 | 12/26/91 | wo . | | <i></i> | |
| | AD | 98 39344 A | 11/09/98 | wo | | | |
| | AE | 98 39343 A | 11/09/98 | wo | | -FIV | ED |
| <u> </u> | AF | 98 39342 A | 11/09/98 | wo | RE | 1 = 20 | |
| | AG | 0 180 276 A1 | 05/07/86 | EP | F | | |
| | АН | 3512781 A1 | 04/10/85 | DE | TECH | CENTER 1 | ,0001 |
| | AI | 0 353 692 B1 | 07.02.90 | EPO . | | | |
| | AJ . | WO 96/01267 A | 18.01.96 | wo | | | |
| | AK | 0 161 955 A | 21.11.85 | EPO | | | · |
| | AL | WO 97/03679 A | 06.02.97 | wo | | | |
| V | AM | 0 338 372 A | 25.10.89 | EPO | | | |
| L DX | AN | 0 481 214 A | 22.04.92 | EPO | V. | | · |

| EXAMINER: | Dones | - 0 | DATE CONSIDERED: | Sp | Hor |
|-----------|------------------------------------|------------|-------------------------|----|-----------------------|
| EYAMINED. | Initial if reference is considered | whather or | mat aitatian ia in aant | I | A STATE AND COOL DOWN |

| | | ρE | COTHER DOCUMES (Including Author, Title, Date, Persont Pages, etc.) |
|--------------|----------|------------|---|
| | 6 | | FEB 1 5 2002 |
| R | 1 | ED O | Alexander et al. "Preparation of 9-(2- Phoenhonomethoxyethyl) Adenine Esters as PECH CENTER 160/20 |
| _ | <u> </u> | AO TENT | Copy of PAPERS ORIGINALLY FILED |
| | | AP | Amin, et al.,"1-Hydroxy-3-(methylpentylamino)-propylidene-1, 1-bisphosphonic Acid as a Potent Inhibitor o Squalene Synthase," Arznemittelforschung. 46(8): 759-762 (1996) |
| | | XA | Atiq, O.T., et al., "Treatment of Unresectable Primary Liver cancer With Intrahepatic Fluorodeoxyuridine and Mitomycin C Through an Implantable Pump," <u>Cancer</u> , 69, 920-924 (1992) |
| | | AQ | Auberson, et al., "N-Phosphoalkyl-5-Aminomethylquinoxaline-2,3-Diones: In Vivo Active Ampa and NMDA(Glycine) Antagonists," Bioorg. Med. Chem. Lett., 9: 249-254 (1999) |
| | | AR | Balthazor, <i>et al.</i> "Nickel-Catalyzed Arbuzov Reaction: Mechanistic Observation," <u>J. Org Chem.,</u> 45: 5425-5426 (1980) |
| | | XB | He, et al., "Inactivation of Cytochrome P450 3A4 by Bergamottin, a Component of Grapefruit Juice," Chem Res. Toxicol 1998, 11, 252-259 |
| | | AS | Bespalov, et al., "Prologation of morphine analgesia by competitive NMDA receptor antagonist D-CPPene (SDZ EAA 494) in rats," Eur. J. Pharmacol. 351: 299-305 (1998) |
| | | AT | Bijsterbosch, <i>et al.</i> , "Disposition of the acyclic Nucleoside Phosphonate (S)-9-(3-Hydroxy-2-Phosphonylmethoxypropyl) Adenine," <u>Antimicrobial Agents and Chemotherapy</u> . 42(5): 1146-1150 (1998) |
| | | AU | Bird, <i>et al.</i> , "Synthesis of Novel <i>N</i> -Phosphonoalkyl Dipeptide Inhibitors of Human Collagenase," <u>J. Med. Chem.</u> 73: 158-169 (1994) |
| | 1 | AV | Brill and Landon, <i>et al.</i> , <u>Chem Rev</u> ., 84: 577-585 (1984) |
| P | } | AW | Campagne, et al. "Synthesis of Mixed Phosphate Diester Analogues of Dipeptides using BOP or PyBOP Reagents," Tetrahedron Lett., 34(42): 6743-6744 (1993) |

| EXAMINER: | Duns | DATE CONSIDERED: | 02 |
|-----------|---|-----------------------------------|-----------------------|
| EXAMINER: | Initial if reference is considered, whether | or not citation is in conformance | e with MPEP 609; Draw |

line through citation if not in conformance and not considered. Include a copy of this form with next communication to applicant

| • . | | 69 1978.454 |
|-----|--------|---|
| | 6 | OTHER DOCUMES (Including Author, Title, Date, Per Pages, etc.) RECEIVE |
| | FEB | FEB I 5 2002 |
| N/ | 1 3/2. | Campbell, "The Synthesis of Phosphonate Esthers, an Extension of the Mitsunobu Realton, Golden Charles |
| 100 | | COPY OF PAPERS ORIGINALLY FILED |
| | AY | Casara, et al., "Synthesis of Acid Stable 5'-o-Fluorometer Phosphonates of Nucleosides," <u>Bioorg. Med.</u> Chem. Lett., 2(2): 145-148 (1992) |
| | AZ | Casteel, et al., "Steric and Electronic Effects in the Aryl Phosphate to Arylphoshonate Rearrangement," Synthesis, 691-693 (1991) |
| | хс | Chen, et al., , "Sensitization of Human Breast Cancer Cels to Cyclophosphamide and Ifosfamide by Transfer of al Liver Cytochrome P450 Gene," Cancer Research, 56, 1331-1340 (1996) |
| | XD | Chen and Waxman "Intratumoral Activation and Enhanced Chemotheraputic Effect of Oxazaphosphorines following Cytochrome P-450 Gene Transfer: Development of a Combined chemptherapy/Cancer Gene Therapy Strategy," Cancer Research, 55, 581-589 (1995) |
| | ВА | De Lombaert, et al., "N-Phosphomomethgyl Dipeptides and Their Phosphonate Prodrugs, a New Generation of Neutral Endopeptidase (NEP, EC 3.4.24.11) Inhibitors" J. Med. Chem 37: 498-511 (1994) |
| | | |
| | ВВ | De Lombaert, et al., "Pharmacological profile of a Non-Peptidic Dual Inhibitor of Neutral Endopeptidase 24.11 and Endothelin-converting enzyme," Biochem Biophys Res Commun 204: 407-412 (1994) |
| | | |
| | ВС | De Waziers, et al., "Cytochrome P 450 Isoenzymes, Epoxide Hydrolase and Glutathione Transferases in Rat and Human Hepatic and Extrahepatic Tissues," J. Pharm. Exp. Ther. 253: 387-394 (1990) |
| | | |
| | BD | Dearfield, et al., "Analysis of the Genotoxicity of Nine Acrylate/Methacrylate Coumpounds in L5178Y Mouse Lymphoma Cells," Mutagenisis 4: 381-393 (1989) |
| | BE | Desos, et al., "Structure-Activity Relationships in a Series of 2(1H)-Quinolones Bearing Different Acidic Function in the 3-Position: 6,7-Dichloro-2(1H)-oxoquinoline-3-phosphonic Acid, a New Potent and Selectiv AMPA/Kainate Antagonist with Neuroprotective Properties," 39: 197-206 (1996) |
| (A) | BF | Dickson, <i>et al.</i> , "Orally Active Squalene Synthase Inhibitors: Bis((acyloxy)alkyl) Prodrugs of the α- Phosphonosulfonic Acid Moiety," <u>J. Med. Chem.</u> 39: 661-664 (1996) |

| EXAMINER: | DATE CONSIDERED: / |
|--|--|
| | \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\ |
| D(1me/) | 921/02 |
| | . () |
| FXAMINER: Initial if reference is considered whether | er or not citation is in conformance with MPEP 600. Draw |

| | | OTHER DOCUME (Including Author, Title, Date, Per anni Pages, etc.) |
|----------|-------------|--|
| DE | 8G | Edmunson, et al., "Cyclic Organophosphorus Compounds. Part 23. Configurational Assignments in the 4-Phenyl-1,3,2λ5-dioxaphosphorinane Series. X-Ray Molecular Structure of cis-2-Benzylamino-4-phenyl-1,3,2-dioxaphosphorinane 2-Oxide," J. Chem. Res. Synop., 5: 122-123 (1989) |
| EB (| | Enriquez, et al.,"Conjugation of Aadenine Arabinoside 5'-Monophosphate to Arabinogalactan: Synthesis, Characterization, and Antiviral Activity," Bioconjugate Chem. 6: 195-202 (1995) |
| PM & TRI | BI | Farquhar, et al. "Biologically-Cleavable Phosphate Protective Groups: 4-Aclioxt-1,3,2-Dioxaphosphorinanes as Neutral Latent Precursors of Dianionic Phosphates," <u>Tetrahedron Lett.</u> , 36(5): 655-658 (1995) |
| | ВЈ | Farquhar, et al., "Biologically Reversible Phosphate-Protective Groups," <u>Journal of Pharmaceutical Sciences</u> 72(3): 324-325 (1983) |
| | ВК | Farquhar, et al., "Synthesis and Biological Evaluation of 9-[5'-(2-Oxo-1,3,2-oxazaphosphorinan-2-yl)-\(\beta\)-\(\beta\)-\(\text{prop}\) arabinosyl]adenine and 9-[5'-(2-Oxo-1,3,2-dioxazaphosphorinan-2-yl)-\(\beta\)-\(\text{D-arabinosyl}\) adenine: Potential Neutral Precursors of 9-[\(\beta\)-D-Arabinofuranosyl]adenine 5'-Monophosphate," \(\text{J. Med. Chem.}\) 28: 1358-1361 (1985) |
| | BL | Farquhar, et al., "Synthesis and Biological Evaluation of Neutral Derivatives of 5-Fluoro-2'-deoxyuridine 5'-Phosphate," J. Med. Chem. 26: 1153-1158 (1983) |
| | ВМ | Fiume, et al., Inhibition of Hepatitis B Virus replication By Vidarbine Monophosphate Conjugated with Lactosaminated Serum Albumin, The Lancet 13-15 (1988) |
| | BN | Freed, et al., "Evidence for Acyloxymethyyl Esters of Pyridmidenc, 5'-Deoxyribonucleotides as extraceullar sources of active a5'-deozyriboinucleotides in cultured cells," Biochemical Pharmacology, 38(19): 3193-3198 (1989) |
| | ВО | Guida, et al.,"Structure-Based Design of Inhibitors of Purine Nucleoside Phosphorylase. 4. A Study of Phosphate Mimics," J. Med. Chem. 37: 1109-1114 (1994) |
| | ∥ BP | Hirayama, et al., "Structure and conformation of a novel inhibitor of angiotensin I converting enzyme – a tripeptide containing phosphonic acid," Int. J. Pept. Protein Res. 38: 20-24 (1991) |
| 18 | BQ | Hunston, et al., "Synthesis and Biological Properties of Some Cyclic Phosphotriesters Derived from 2'- Deoxy-5-fluorouridine," J. Med. Chem. 27: 440-444 (1984) |

| EXAMINER: | DATE CONSIDERED: 8/2/62 |
|--|-------------------------|
| EXAMINER: Initial if reference is considered, whether or line through citation if not in conformance and not considered. | |

communication to applicant

| | • | , | OTHER DOCUME (Including Author, Title, Date, Per ent Pages, etc.) |
|------|----------|------------|--|
| , | | | ORIGINALLY FILE. |
| R | <u> </u> | BR | Keenan, et al., "Pathology Reevaluation of the Kociba et al. (1978) Bioassay of 2,3,7,8-TCDD: Implications for Risk Assessment," J. Tox. Envir. Health 34: 279-296 (1991) |
| P | | 3 5 | Kelley, et al., "[[(Guaninylalkl) phosphinico] methyl] phosphonic Acids. Multisubstrate Analogue inhibitors o Human Erythrocyte Purine Nucleoside Phosphorylase," J. Med. Chem. 38: 1005-1014 (1995) |
| EB 0 | 8 700° | OFFICE | Khamnei and Torrence, "Neighboring Group Catalysis in the Design of Nucleotide Prodrugs," <u>J. Med. Chem.</u> 39: 4109-4115 (1996) |
| | | BU | Kryuchkov, <i>et al.</i> , <u>Izv. Akad. Nauk SSSR, Ser. Khim.</u> 6: 1201-1248 (1987) |
| | | BV | Lok, et al., "Neurotoxicity associated with adenine arabinoside monophosphate in the treatment of chronic hepatitis B virus infection," J. Antimicrob. Chemotherap. 14: 93-99 (1984) |
| | | BW | Lu et al., "Palladium-Catalyzed Reaction of Aryl Polyfluoroalkanesulfonates with O,O-Dialkyl Phosphonates Synthesis, 726-727 (1987) |
| | | вх | McGuigan, et al., "Kinase Bypass: A new strategy for Anti-Hiv Drug Design," Bioorganic & Medicinal Chemistry Letters, 3(6): 1207-1210 (1993) |
| | | BY | Meier, et al., "Cyclic Saligenyl Phosphotriesters of 2',3'-Dideoxy-2'3'-didehydrothymidine (d4t)," Bioorganic & Medicinal Chemistry Letters, 7(2): 99-104 (1997) |
| | | BZ | Meijer, et al.,"Covalent and Noncovalent Protein Binding of Drugs: Implications for Hepatic Clearance, Storage, and Cell-Specific Drug Delivery," Pharm. Res. 6: 105-118 (1989) |
| | | CA | Melvin, "An Efficient Synthesis of 2-Hydroxyphenylphosphonates," <u>Tetrahedron Lett.</u> , 22(35): 3375-3376 (1981) |
| - | | CB | Meyer, et al., "2"-O'-Acyl-6-thioinosine Cyclic 3', 5'-Phosphates as Prorugs of Thioinosinic Acid," J. Med. |

| EXAMINER: < | Dane | DATE CONSIDERED: | 21/ | 0 |
|-------------|------|------------------|-----|---|
| | | | | |

| | • | | OTHER DOCUME (Including Author, Title, Date, Per Int Pages, etc.) COPY OF PAR ORIGINALLY F |
|---|----------|--|--|
| 1 | X | СС | Mitchell, et al., "Bioreversible Protection for the Phospho Group: Bioactivation of the Di(4-acyloxybenzyl) and Mono(4-acyloxybenzyl) Phosphoesters of Methlphosphonate and Phosphonoacetate," J. Chem. Soc. Perkin Trans. 1 |
| 0 | PE | 100 | Mitsunobu, "The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformatio of Natural Products," Synthesis, 1-28 (1981) |
| | O 8 Z | A STATE OF THE PARTY OF THE PAR | Moore, et al., "Comparison of Mutagenicity results for Nine Coumpounds exaluated at the hgprt Locus in the Standard and Suspension CHO Assays," Mutagenisis 6: 77-85 (1991) |
| ` | | XE | Murray, et al., "Cytochrome P450 Expression is a common Molecular Event in Soft Tissue Sarcomas," <u>J. Pathology</u> , 171, 49-52 (1993) |
| | | XF | Murray, et al., "Cytochrome P450 CYP3A in human renal cell cancer," <u>British J. Cancer</u> , 79, 1836-1842 (1999) |
| | | CF | Neidlein, et al., "Mild Preparation of 1-Benzyloxyiminoalkylphosphonic Dichlorides: Application to the Synthesis of Cyclic Phosphonic Deisters and Cyclic Monoester Amides," Heterocycles 35: 1185-1203 (1993) |
| | - | cG | Nifantyev, et al.,"Synthesis and Structure of Some Stable Phospholane-Phospholanes," Phosphorus, Sulfu Silicon and Related Elements 113: 1-13 (1996) |
| | <u>.</u> | XG | Ogg, et al., <u>Xenobiotica</u> 29, 269-279 (1999) |
| | | СН | Ohashi, et al., "Synthesis of Phosphonosphingoglycolipid found in Marine Snail Turbo Comutus," Tetrahedron Lett., 29(10): 1189-1192 (1988) |
| | | а | Petrakis, et al., Palladium-Catalyzed Substitutions of Triflates Derived from Tyrosine-Containing Peptides and Simpler Hydroxyarenes Forming 4-(Diethoxyphosphinyl) phenylalanines and Diethyl Arylphosphonates," J. Am. Chem. Soc., 109: 2831-2833 (1987) |
| 7 | 9 | а | Redmore, "Phosphorus Derivatives of Nitrogen Heterocycles," <u>J. Org. Chem.</u> , 35(12): 4114-4117 (1970) |

| EXAMINER: | Mores | DATE CONSIDERED: | /D |
|-----------|-------|------------------|----|
| | | | |

| | • | 9 22 57 |
|-----------------------------------|------|---|
| | | OTHER DOCUME (Including Author, Title, Date, Per Int Pages, etc.) COPY OF PAPERS |
| | | ORIGINALLY FILED |
| $\sqrt{\ \ }$ | | |
| LL | / | C |
| $\frac{\mathcal{L}}{\mathcal{L}}$ | CK | Shaw & Cundy, "Biological Screens of PMEA Prodrugs," Pharm. Res. 10 (supp) s24 (1993) |
| _/} \ | - | |
| | ĺ | Shih, et al., "Preparation and Structures of 2-Dimethylamino-4-phenyl-1,3,2-dioxaphosphorinane-2-oxides |
| PE | CL | Bull. Inst. Chem. Acad. Sin, 41: 9-16 (1994) |
| | * | |
| B 0 8 20 | 2 2 | Turner "A Constal Approach to the Synthesis of 1.6. 1.7. and 1.9 North widings " 1. Ora Chara EE/4E |
| 8 9 | G. | Turner, "A General Appproach to the Synthesis of 1,6-,1,7-, and1,8-Naphthyridines," <u>J. Org. Chem.</u> 55(15) (1990) |
| | 187 | |
| G TRAD | | |
| | 1 | Venook, A.P, "Treatment of Heptacellular Carcinoma: Too Many Options?" <u>J. Clin. Oncol</u> . 12, 1323-1334 |
| | XH | (1994) |
| | | |
| | | Vo-Quang, et al., "(1-Amino-2-propenyl) Phosphonic Acid, an Inhibitor of Alanine Racemase and D- |
| | CN | Alanine:D-Alanine Ligase.," <u>J. Med. Chem.</u> 29(4): 579-581 (1986) |
| | | |
| | | Wagner, et al., "Direct Conversion of Tetrahydropyranylated Alcohols to the corresponding Bromides," |
| | co | Tetrahedron Letters 30(5): 557-558 (1989) |
| | | |
| | | Wallace, et al., "Design and Synthesis of Potent, Selective Inhibitors of Endothelin-Converting Enzyme," J |
| | СР | Med. Chem. 41: 1513-1523 (1998) |
| | | |
| | | |
| | co | Walsh, et al., "The Structures of Grantianine and Sceleratine," J. Am. Chem. Soc., 78: 4455-4458 (1956) |
| | 134 | (100) |
| | | |
| | \ \r | Walking at at Photographics 4 474 494 (4004) |
| | XI | Watkins, et al., Pharmacogenetics 4, 171-184 (1994) |
| | | Weibel, et al., "Potentiating Effect of {2-[2-[(2-Amino-1,6-Dihydro-6-oxo-9H-Purin-9-yl)Methyl]-Phenyl]-Phosphonic Acid (MDL 74,428), A Potent Inhibitor of Purine Nucleoside Phosphorylase, of Purine Nucleoside |
| \mathcal{M} | | the Antiretroviral Activities of 2', 3'- Dideoxyinosine Combined to Ribavirin in Mice," Biochem. Pharmacol. |
| | CR | 48(2):245-252 (1994) |
| 4) | | |
| μ | | |
| . 1 | cs | Wileman, et al., "Receptor – mediated endocytosis," Biochem. J. 232: 1-14 (1985) |

| EXAMINER: | | in) | DATE CONSIDERED: | /2/ | 0 |
|-----------|--------|------|------------------|-----|---|
| | τ | 7 | - | ′ / | |

| N | x | Yu, et al., "In Vivo Modulation of alternative Pathways of P-450-Catalyzed Cyclophosphamide Metabolism Impact on Pharmacokinetics and Antitumor Activity," <u>J. Pharm. Exp. Ther.</u> 288, 928-937 (1999) |
|--------|--------------|--|
| E JON | •ेट <u>ा</u> | Zon, "Cyclophosphamide Analogues," <u>Progress in Med Chem</u> . 19: 1205-1246 (1982) |
| & TAME | A CONTRACTOR | Predvoditelev D., et al., "Glycero-2-hydroxymethylene phosphates" <u>Journal of Organic Chemistry of the USSR (English Translation</u> 13:1489-1492 (1977) |
| 8 Inn | cv | Predvoditelev, D. et al., "Synthesis of lipids and their models on the basis of glycerol alkylene phosphites V. Cyclic phosphatidylglycerol and phosphatidylhydroxyhomocholine" <u>Journal of Organic Chemistry of the USSR (English Translation</u> 17:1156-1165 (1981) |
| 1 | cw | Hillers, et al., "Analogs of pyrimidinemono- and polynucleotides. VI. Phosphates of 1-(1,4-dihydroxy-2-pentyl) thymine and 1-(1,3-dihydroxy-2-propyl) uracil" 89 (17): 1-264 (1978) |
| N N | α | Farquhar, et al., "5'-'4-(Pivaloyloxy)-1, 3, 2-dioxaphosphorinan –2-y]-2'-deoxy-5-fluorouridine: a membran permeating prodrug of 5-fluoro-2'-deoxyuridylic acid (FDUMP)" Journal of Medicinal Chemistry 38:488-49 (1995) |

COPY OF PAPERS ORIGINALLY FILED **RECEIVED**

FEB 1 5 2002

TECH CENTER 1600/2900

| EXAMINER: | • |
|-----------|---|
| | t |
| | |

DATE CONSIDERED: